CARDIOVASCULAR MEDICINE

Magnitude and consequences of undertreatment of high-risk patients with non-ST segment elevation acute coronary syndromes: insights from the DESCARTES Registry

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Objective: To analyse intensity of treatment of high-risk patients with non-ST elevation acute coronary syndromes (NSTEACS) included in the DESCARTES (Descripción del Estado de los Sindromes Coronarios Agudos en un Registro Temporal Español) registry.
Patients and setting: Patients with NSTEACS (n = 1877) admitted to 45 randomly selected Spanish hospitals in April and May 2002 were studied.
Design: Patients with ST segment depression and troponin rise were considered high risk (n = 478) and were compared with non-high risk patients (n = 1399).
Results: 46.9% of high-risk patients versus 39.5% of non-high-risk patients underwent angiography (p = 0.005), 23.2% versus 18.8% (p = 0.038) underwent percutaneous revascularisation, and 24.9% versus 7.4% (p < 0.001) were given glycoprotein IIb/IIIa inhibitor. In-hospital and six-month mortality were 7.5% versus 1.1% and 17% versus 4.6% (p < 0.001), respectively. A treatment score (⩾ 4, 2–3 and < 2) was defined according to the number of class I interventions recommended in clinical guidelines: aspirin, clopidogrel, β blockers, angiotensin-converting enzyme inhibitors, statins and revascularisation. Independent predictors of six-month mortality were age (odds ratio (OR) 1.07, 95% confidence interval (CI) 1.04 to 1.10, p < 0.001), diabetes (OR 1.92, 95% CI 1.14 to 3.22, p = 0.014), previous cardiovascular disease (OR 4.17, 95% CI 1.63 to 10.68, p = 0.003), high risk (OR 2.20, 95% CI 1.30 to 3.71, p = 0.003) and treatment score < 2 versus ⩾ 4 (OR 2.87, 95% CI 1.27 to 6.52, p = 0.012).
Conclusions: Class I recommended treatments were underused in high-risk patients in the DESCARTES registry. This undertreatment was an independent predictor of death of patients with an acute coronary syndrome.

Patients presenting with non-ST elevation acute coronary syndromes (NSTEACS) are a heterogeneous group with wide differences in prognosis. Thus, patient stratification is mandatory to use correctly the different treatment approaches to reduce morbidity and mortality. ST segment depression and release of biomarkers of necrosis are two of the clinical characteristics readily available at hospital admission, and their effectiveness in predicting outcomes has been confirmed in previous reports. In the PEPA (Proyecto de Estudio del Pronostico de la Angina) study the relative risk of mortality at 90 days for patients presenting with ST segment depression was 1.45 compared with those with normal ECG.[1] The FRISC II (FRagmin and Fast Revascularisation during InStability in Coronary artery disease) investigators reported that ST segment depression at admission also determined an 8% absolute increase in the risk of death or myocardial infarction at one year and that an invasive strategy improved survival.[2] Similarly, troponin release during angina has been shown to be a marker of the degree of coronary artery disease; higher concentrations correlated with three-vessel disease, the presence of intracoronary thrombus, total coronary occlusion and ejection fraction < 45%. Release of troponins is also associated with an increased risk of reinfarction and death during follow up.[3] In the FRISC trial, the level of troponin release was associated with higher two-year mortality. When ST segment depression was also present, mortality more than doubled for each troponin risk level.[4]

Several trials have shown that an invasive strategy, including coronary revascularisation[5–7] and administration of glycoprotein IIb/IIIa inhibitors,[8] in the treatment of high-risk patients with NSTEACS improves prognosis. On the basis of these data, clinical guidelines recommend an invasive strategy as a class I indication in high-risk patients. The DESCARTES (Descripción del Estado de los Sindromes Coronarios Agudos en un Registro Temporal Español) registry was undertaken to analyse the clinical characteristics, treatment and outcomes of a representative sample of patients with NSTEACS admitted to Spanish hospitals.[9] We studied the intensity of drug treatment at discharge and in-hospital revascularisation and how they relate to outcomes of the patients at highest risk included in the DESCARTES registry.

METHODS

The DESCARTES methods have been described previously.[9] In brief, all patients with suspected NSTEACS (excluding those with left bundle branch block or permanent pacing)

Abbreviations: ACE, angiotensin-converting enzyme; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; DESCARTES, Descripción del Estado de los Sindromes Coronarios Agudos en un Registro Temporal Español; FRISC II, FRagmin and Fast Revascularisation during InStability in Coronary artery disease; GRACE, Global Registry of Acute Coronary Events; NSTEACS, non-ST elevation acute coronary syndromes; PCI, percutaneous coronary intervention; PEPA, Proyecto de Estudio del Pronostico de la Angina

admitted to 45 randomly selected Spanish hospitals (see appendix) between April and May 2002 were prospectively enrolled and followed up for six months.

Patients were divided into two groups: high-risk patients, who presented with dynamic ST changes at admission ECG and had raised myocardial necrosis markers (troponins or creatine kinase MB fraction); and non-high-risk patients, with neither of those features.

Data collection and management

Recorded variables were clinical characteristics, ECG changes, laboratory measurement of myocardial necrosis markers and lipids, in-hospital admission location (emergency department, general ward, intensive care unit or step-down intensive care unit), clinical evolution, and in-hospital and discharge treatments. Data were electronically recorded and sent after encryption to the coordinating centre (Institut Municipal d'Investigació Mèdica-Barcelona) by email.

Follow up

Patients were followed up at six months by telephone call. The recorded outcomes were death (cardiac or non-cardiac) and hospital readmission.

Quality control

All centres had to meet the following requirements at the completion of the study: (1) registration of at least 70% of patients with NSTEACS admitted to the hospital (coverage rate); (2) registration of more than 75% of patients with NSTEACS admitted to the treating department (exhaustivity rate); and (3) sufficient concordance (that is, κ statistic $> 70\%$) in 10 key variables with those obtained by external monitors from medical records. Among hospitals contributing data for 40 or fewer patients, quality of selected variables was controlled for each patient; in higher recruiting hospitals the same variables were controlled for 40 randomly selected patients.

Statistical analysis

Survivors to 28 days were chosen to explore long-term effectiveness of in-hospital revascularisation, because patients who died within this period, did so very early in the hospital phase and before they had a chance to undergo cardiac catheterisation.

Differences in variables between high-risk and non-high-risk patients and between dead and surviving patients within the high-risk group were assessed by the χ^2 test for categorical variables and by Student's t test or Mann–Whitney U test as appropriate for continuous variables. Continuous variables are presented as mean (SD) and categorical variables as percentages. The adjusted hazard ratios of six-month mortality for 28-day survivors were estimated by a proportional hazards Cox model analysis. The models assessed the impact of treatment on outcomes adjusted for age, diabetes, hypertension, history of cardiovascular disease and high-risk feature. A treatment score was developed according to the number of class I recommended treatments for NSTEACS received under clinical guidelines: aspirin, clopidogrel, β blockers, angiotensin-converting enzyme (ACE) inhibitors and statins (drugs at discharge), and coronary revascularisation (in hospital) by adding one point for each drug. The score was then categorised in the groups (≥ 4, 2–3, < 2) according to the best area under the receiver operating characteristic curve.

RESULTS

In the non-high-risk group, 18.2% (254 of 1399) of patients had ST changes without troponin rise and 31.6% (442 of 1399) had raised biomarkers without ST changes.

High-risk group

Tables 1 and 2 show the clinical characteristics, admission variables, diagnostic procedures and outcomes for the 478 high-risk and 1399 non-high-risk patients. Compared with the non-high-risk group, high-risk patients were significantly older and had higher prevalence of insulin-treated diabetes. On admission, fewer high-risk patients were taking β blockers (21.8% *v* 29.3%, $p = 0.002$) and statins (27.6% *v* 35.2%, $p = 0.002$) but they did not differ in previous aspirin, clopidogrel, calcium channel blocker, nitrate or ACE inhibitor administration. Admission chest pain lasted longer and heart rate was higher in the high-risk group. More than 50% of high-risk patients were initially admitted to an intensive care unit (coronary or general), but the other half were managed either in the emergency department or in a general ward. ST segment depression was present in 88.9% and transient ST segment elevation in 11.1% of high-risk patients but in only 15.6% and 3.0%, respectively, of the non-high-risk group. High-risk patients had significantly lower ejection fraction and a higher prevalence of multivessel and left main coronary disease. Mortality at 28 days was significantly higher in the high-risk group (7.5% *v* 1.1%, $p < 0.001$). Despite troponin rise in every high-risk patient, unstable angina was the discharge diagnosis in 27.5% and non-ischaemic chest pain in 3.8% of these patients.

High-risk patients received significantly more antithrombotic agents in hospital, including glycoprotein IIb/IIIa inhibitors; 109 high-risk patients underwent percutaneous coronary intervention (PCI) and 45 of them (41.3%) received glycoprotein IIb/IIIa inhibitors. Of the 118 high-risk patients who received glycoprotein IIb/IIIa inhibitors, 58 underwent PCI or coronary artery bypass grafting (49.2%). The rest were not treated invasively. High-risk patients also received more ACE inhibitors and nitrates and fewer calcium channel blockers. No differences were seen in the administration of β blockers and statins. A higher percentage of high-risk patients underwent PCI or coronary bypass graft. Prescription of β blockers and of statins at discharge did not differ (table 3).

Among high-risk patients, significantly more six-month survivors received aspirin plus clopidogrel (41.6% *v* 23.7%, $p = 0.004$) and β blockers (65% *v* 43.4%, $p < 0.001$) in hospital and underwent coronary angiography (50.9% *v* 28.6%, $p < 0.001$) and PCI (26.1% *v* 7.9%, $p = 0.001$). At discharge, significantly more survivors also received clopidogrel (40.4% *v* 17.1%, $p = 0.007$), β blockers (58.8% *v* 26.5%, $p < 0.001$) and statins (62.5% *v* 38.2%, $p = 0.006$).

Treatment intensity and survival

To analyse treatment intensity as recommended in the clinical guidelines and its impact on six-month mortality, 271 patients with a discharge diagnosis of chest pain of non-ischaemic origin and a centrally read normal ECG were excluded, leaving 1606 patients for this analysis.

Diabetes, hypertension and previous cardiovascular disease were associated with a higher treatment intensity score, whereas age was inversely related. High-risk classification did not correlate with treatment intensity. Six-month mortality was associated with a lower intensity of treatment (table 4). Figure 1 shows Kaplan–Meier survival curves for high-risk and non-high-risk groups; survival at six months was 83.0% and 95.4% ($p < 0.001$), respectively. Figure 2 shows survival curves for non-high-risk and high-risk groups by treatment score: survival at six months was 98.6%, 83.4%, 60% and 95.4% ($p < 0.001$) for high-risk treatment scores ≥ 4, 2–3 and < 2 and for non-high-risk patients, respectively. Table 5 shows the adjusted hazard ratios and 95% confidence intervals of six-month mortality for patients who survived 28 days. Independent predictors of death were age,

Table 1 Clinical characteristics and admission variables of patients with non-ST elevation acute coronary syndromes divided by level of risk

	High risk		
	No (n = 1399)	Yes (n = 478)	p Value
Age (years)	66.1 (11.4)	69.6 (12.1)	<0.001
Women	460 (32.9%)	172 (36.0%)	0.215
Cardiovascular risk factors			
Family history	388 (28.0%)	111 (23.3%)	0.048
Smoking			0.297
Current	267 (19.4%)	107 (22.8%)	
Former	427 (31.1%)	138 (29.4%)	
Diabetes mellitus	414 (29.9%)	160 (33.8%)	0.110
Insulin treated	120 (29.1%)	75 (47.2%)	<0.001
Hypertension	826 (59.7%)	303 (64.3%)	0.074
Dyslipidaemia	745 (54.3%)	223 (47.6%)	0.013
Previous cardiovascular disease	1029 (74.0%)	337 (70.8%)	0.170
Angina	740 (53.5%)	212 (44.6%)	0.001
Myocardial infarction	428 (30.9%)	127 (26.8%)	0.093
Cerebrovascular accident	98 (7.1%)	58 (12.2%)	<0.001
Peripheral arterial disease	106 (7.7%)	68 (14.4%)	<0.001
Congestive heart failure	120 (8.6%)	71 (15.0%)	<0.001
Percutaneous coronary intervention	236 (17.0%)	37 (7.8%)	<0.001
Coronary artery bypass graft	130 (9.4%)	35 (7.4%)	0.185
Chest pain duration (min)	30 (15–90)	60 (20–140)	<0.001
Heart rate at admission (beats/min)	73 (63–85)	84 (71–100)	<0.001
Initial admission site (% valid)			<0.001
Cardiology ward	741 (53.2%)	142 (29.7%)	
Emergency department	282 (20.2%)	63 (13.2%)	
Coronary care unit	154 (11.1%)	167 (34.9%)	
General intensive care unit	107 (7.7%)	75 (15.7%)	
Other	109 (7.8%)	31 (6.5%)	
ECG at admission (% valid)			<0.001
ST segment depression	213 (15.6%)	425 (88.9%)	
Normal repolarisation	445 (32.6%)	0 (0.0%)	
Negative T wave	368 (26.9%)	0 (0.0%)	
Non-specific repolarisation changes	299 (21.9%)	0 (0.0%)	
ST segment elevation (transient)	41 (3.0%)	53 (11.1%)	
Hospital stay (days)	7 (4–11)	9 (6–13)	<0.001

Data are mean (SD), median (25th to 75th centile) of number (%). Percentages are calculated on available data.

diabetes, previous cardiovascular disease, high risk and intensity of treatment. Even after the independent predictive clinical variables were entered in the model, patients who received fewer than two class I treatments had an almost three times higher probability of dying at six months than those who were managed with an optimal number of interventions.

DISCUSSION

High-risk patients with NSTEACS were largely undertreated in the DESCARTES Registry performed in Spain in 2002. Fewer than half of these patients underwent coronary angiography and roughly one third were revascularised during the index hospitalisation. In addition, the rate of

Table 2 In-hospital diagnostic procedures and outcomes

	High risk		
	No (n = 1399)	Yes (n = 478)	p Value
Diagnostic procedure			
Echocardiographic studies	725 (52.3%)	310 (65.0%)	<0.001
Ejection fraction <40%	102 (11.5%)	59 (16.3%)	0.023
Non-invasive ischaemia detection test	619 (44.6%)	114 (24.0%)	<0.001
Coronary angiography	548 (39.5%)	224 (46.9%)	0.005
Early (<48 h)	117 (8.5%)	86 (18.2%)	<0.001
Significant vessel disease	429 (80.6%)	194 (89.0%)	0.006
1 vessel	171 (32.2%)	52 (23.9%)	<0.001
2 vessels	130 (24.5%)	62 (28.4%)	
3 vessels	128 (24.1%)	79 (36.2%)	
Left main disease	41 (7.9%)	28 (13.8%)	0.015
Lipid measurement	1053 (75.7%)	399 (83.5%)	<0.001
In-hospital complication			
AMI/reinfarction	46 (3.3%)	49 (10.3%)	<0.001
Congestive heart failure	85 (6.1%)	97 (20.5%)	<0.001
Death	15 (1.1%)	36 (7.5%)	<0.001
Discharge diagnosis by attending physician			<0.001
Unstable angina	846 (61.6%)	130 (27.5%)	
Non-Q wave AMI	187 (13.6%)	290 (61.3%)	
Q wave AMI	26 (1.9%)	35 (7.4%)	
Non-ischaemic/unknown origin of chest pain	314 (22.9%)	18 (3.8%)	

Data are mean (SD) of number (% studied patients). Percentages are calculated on available data.
AMI, acute myocardial infarction.

Table 3 In-hospital and discharge treatment

	High risk		
	No (n = 1399)	Yes (n = 478)	p Value
Drug treatment (in hospital)			
Aspirin	1196 (86.5%)	431 (90.5%)	0.022
Heparin	1066 (77.5%)	440 (92.4%)	<0.001
Clopidogrel	473 (34.5%)	215 (45.4%)	<0.001
Glycoprotein IIb/IIIa inhibitors	102 (7.4%)	118 (24.9%)	<0.001
β blockers	872 (63.4%)	288 (60.8%)	0.310
ACE inhibitors	595 (43.3%)	254 (53.7%)	<0.001
Statins	713 (51.8%)	253 (53.6%)	0.503
Calcium channel blockers	599 (43.4%)	172 (36.3%)	0.007
Nitrates	1172 (84.6%)	428 (89.9%)	0.004
Revascularisation procedures (during admission)			
Percutaneous coronary intervention	256 (18.8%)	109 (23.2%)	0.038
Coronary artery bypass graft	44 (3.2%)	33 (7.0%)	<0.001
Discharge treatment			
Aspirin	1014 (74.1%)	357 (78.6%)	0.051
Clopidogrel	404 (29.7%)	171 (37.8%)	0.001
β blockers	749 (55.0%)	244 (53.9%)	0.665
ACE inhibitors	531 (39.0%)	205 (45.4%)	0.016
Patients with class I indication	433 (49.2%)	167 (51.9%)	0.414
Statins	739 (54.1%)	250 (55.4%)	0.633
Patients with class I indication	707 (58.3%)	232 (58.1%)	0.961

ACE, angiotensin converting enzyme. Percentages are calculated on available data.

use of β blockers, statins and ACE inhibitors was low and only one in four patients was treated with a glycoprotein IIb/IIIa inhibitor. Undertreatment of high-risk NSTEACS is independently associated with higher six-month mortality.

Patient characteristics and treatments

As there are some discrepancies between guidelines in the definition of high-risk patients,[10–12] we arbitrarily set an undisputable definition of high risk for this study. The definition of high risk, combining ST segment depression and troponin rise, was chosen to unequivocally identify a high-risk group as previously shown by other investigators.[4 13] A treatment score was developed to assess in this population-based registry of NSTEACS the use of class I guideline-recommended treatments and its impact on mortality. Our definition of high risk for the present analysis did not include any other clinical characteristics with known impact on mortality. Nevertheless, these patients were significantly older, had more severe diabetes and had an incidence of previous stroke, peripheral artery disease and congestive heart failure twice that of patients in the non-high-risk group.

Although high-risk patients presented with a longer duration chest pain and higher heart rates, only half of them were admitted to intensive care units and almost 20% were treated in the emergency department or other wards in the hospital; other investigators have reported similar proportions.[14 15] Because adverse outcomes are so common, an intensive care environment has been recommended for this group of patients.[16]

The guidelines recommend treating high-risk patients with an intensive antithrombotic regimen. However, our data confirm that application of the guidelines in the real world is far from optimal, especially in the case of glycoprotein IIb/IIIa inhibitors, which are given to less than 25% of patients. Although guidelines also recommend revascularisation, our results show an important gap in compliance: coronary angiography was done in fewer than half of high-risk patients and only 18% of the procedures were done within 48 h. Similar results have been reported recently by the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines) investigators.[13] We also found a notable underuse of β blockers, ACE inhibitors and statins. We documented that older patients received significantly less intense treatment, that a high risk was not associated with a higher treatment score, and that six-month mortality increased with less adequate treatment. Of note in our registry, high-risk patients who received four or more class I interventions had a survival rate comparable with that of non-high-risk patients, whereas survival was significantly lower for patients who received fewer than two treatments. This finding concurs with a significant beneficial effect of evidence-based drug treatments on survival of patients with acute coronary syndromes observed previously.[17 18]

Table 4 Clinical characteristics and six-month mortality of patients according to treatment score

	≥4 (n = 491)	2–3 (n = 775)	<2 (n = 275)	p for trend
Age (years)	64.9 (11.5)	67.8 (11.1)	70.7 (12.3)	<0.001
Diabetes	170 (34.7%)	238 (31.0%)	72 (26.5%)	0.018
Hypertension	328 (66.9%)	477 (62.2%)	135 (50.0%)	<0.001
Previous CVD	385 (78.6%)	581 (75.3%)	175 (64.1%)	<0.001
High-risk group	144 (29.3%)	213 (27.5%)	74 (26.9%)	0.431
Mortality at 6 months	11 (2.4%)	37 (5.1%)	19 (7.6%)	0.001
Age-adjusted 6-month mortality	2.9% (0.8–4.9%)	4.9% (3.4–6.3%)	6.9% (4.3–9.5%)	0.052

Data are mean (95% CI) or number (%).
CVD, cardiovascular disease.

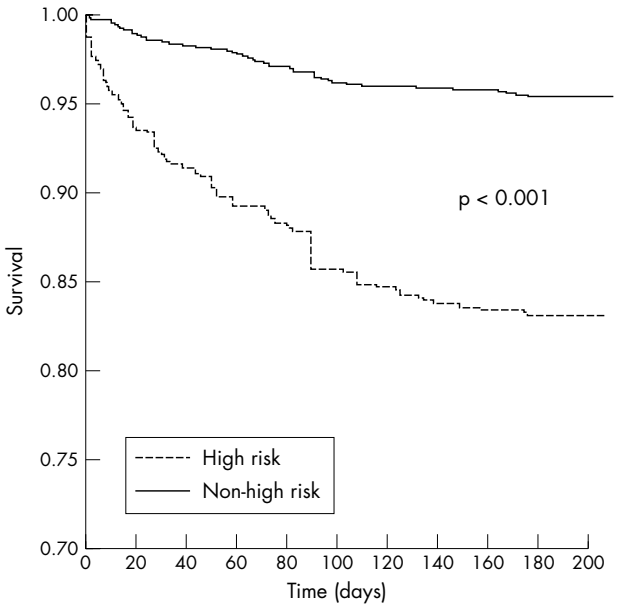

Figure 1 Kaplan–Meier survival curves for high-risk (dashed line) and non-high-risk groups (continuous line). Differences assessed by log rank test.

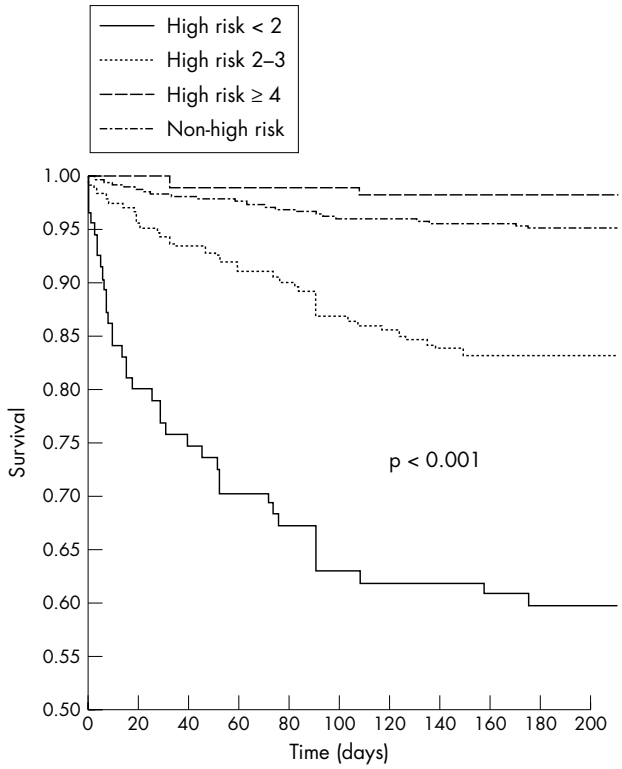

Figure 2 Kaplan–Meier survival curves for high-risk treatment score groups (⩾ 4, 2–3 and < 2) and the non-high-risk group. Curve differences measured by log rank test.

Comparison with other registries

Investigators for the National Registry of Myocardial Infarction described a low early use of glycoprotein IIb/IIIa inhibitors, which were given to only 25% of patients; they also found that hospitals using these drugs had lower adjusted mortalities than hospitals that did not.[19] GRACE (Global Registry of Acute Coronary Events) also reported an overall usage of glycoprotein IIb/IIIa inhibitors in 20%, coronary angiography in 53%, and PCI during index admission in 28% of a group of patients with non-ST segment elevation myocardial infarction. Although these figures compare quite well with our data, the design of the DESCARTES registry to collect data from randomly selected hospitals, as compared with voluntary participation in GRACE,[20] implies a truly more representative sample for the DESCARTES results. Moreover, data from CRUSADE also support our finding that elderly patients, women, patients with diabetes and patients with congestive heart failure received less guideline-compliant treatment and that the presence of raised troponin concentrations, a marker of risk, did not result in an increase of coronary angiography.[21]

Future directions

There is a clear need to improve early risk stratification in NSTEACS and to deliver the intensity of treatment that will reduce in-hospital complications and improve survival. Some physicians are definitely concerned about the application of guideline recommendations to non-selected high-risk patients with other concomitant co-morbidities, who are generally excluded from clinical trials, although there is already ample evidence of improved outcomes when the guidelines are applied to the routine treatment of non-selected patients admitted to general hospitals.[13 19 22] Further studies assessing effectiveness in known environments will help to dispel doubts in this area.[23]

Characteristics and limitations of the present study

Although the methods used in DESCARTES, with random selection of participating hospitals, assures that data reported truly represent treatment of NSTEACS in Spain, our analysis may have several limitations. Firstly, an arbitrary definition of high risk has been used for this study. Although the poor prognosis of patients with ST segment changes and troponin rise is well known, other high-risk patients, such as those with clinical or haemodynamic instability, may have been excluded. However, the potential effect of this lack of specificity would be to attenuate the differences in prognosis and treatment intensity between high-risk and non-high-risk groups and therefore does not substantially alter our findings. Secondly, the selection of treatment intensity score may be biased. Factors such as co-morbidity among older patients or contraindications for each considered treatment may account for differences in survival. Lastly, the DESCARTES study was performed in 2002. By that time the available national guidelines already recommended giving intensive antithrombotic agents and revascularisation for high-risk patients with NSTEACS, although data on clopidogrel administration were less consistent then.[24 25]

Conclusions

A large proportion of high-risk patients with NSTEACS in Spain do not receive the treatment recommended by clinical

Table 5 Adjusted hazard ratios and 95% confidence intervals for six-month mortality for 28-day survivors

	p Value	HR	95% CI
Age	<0.001	1.07	1.03 to 1.10
Diabetes	0.009	1.91	1.17 to 3.10
Hypertension	0.650	1.13	0.66 to 1.96
Previous CVD	0.003	3.96	1.58 to 9.92
High risk	0.002	2.18	1.33 to 3.58
Treatment score <2	0.029		
2–3	0.257	0.72	0.40 to 1.27
⩾4	0.008	0.32	0.14 to 0.74

practice guidelines. The underuse of these treatments is associated with higher six-month mortality. Interventions to improve early risk stratification and proportional treatment of patients with NSTEACS are urgently needed.

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APPENDIX

HOSPITALS AND PRINCIPAL INVESTIGATORS

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